

Tests aiding diagnosis of monogenic diabetes

M Shepherd^{1,2}, **K Colclough**³, **TJ McDonald**^{1,4}

1. Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter UK.
2. Exeter NIHR Clinical Research Facility, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
3. Molecular Genetics Laboratory, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
4. Blood Sciences, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK.

Maggie Shepherd RGN, PhD, Honorary Clinical Professor

Kevin Colclough BSc, Clinical Scientist

Tim McDonald PhD, Consultant Clinical Scientist/ NIHR Clinical Senior Lecturer

Corresponding author:

Maggie Shepherd

L3.11, RILD

Barrack Road

Exeter, EX6 7QX

01392 408261

m.h.shepherd@exeter.ac.uk

Vignette

Daniel was diagnosed with diabetes at the age of 21. He was slim with a BMI of 20 kg/m², presenting blood glucose was 15mmol/L, HbA1c 68mmol/mol (8.4%) and he reported symptoms of polyuria, polydipsia, nocturia and lethargy. He was given a diagnosis of Type 1 diabetes and was started immediately on basal bolus insulin. His mother was diagnosed with Type 1 diabetes at 26 years of age and she had always been insulin treated. His maternal grandfather, who was slim, was diagnosed with Type 2 diabetes in his 40s and was treated with Metformin.

It was 7 years later when Daniel moved to another area that his local Genetic Diabetes Nurse questioned his diagnosis of Type 1 diabetes. This was due to the autosomal dominant family history of diabetes and the fact that he remained on small doses of insulin (0.3u/kg/day) with good glycaemic control HbA1c 48mmol/mol; 6.5%) despite admitting to omitting insulin on some occasions. His details were entered into the MODY probability calculator (<http://www.diabetesgenes.org/content/mody-probability-calculator>) which indicated a 1 in 13 chance of Daniel having Maturity Onset Diabetes of the young (MODY). This reflected an increased chance compared to the background prevalence of 1 in 143. As identifying a genetic diagnosis could potentially change Daniel's treatment, further tests were undertaken.

Islet autoantibodies to glutamate decarboxylase (GAD) and islet antigen-2 (IA-2) antibodies and Zinc transporter 8 (ZnT8) were tested and were all negative, increasing the suspicion that his diabetes may have a non-autoimmune cause. His Urinary C-Peptide Creatinine Ratio (UCPCR) seven years post diagnosis was 1.70nmol/mol, indicating that Daniel was continuing to make significant endogenous insulin which would not be expected in longstanding Type 1 diabetes. As a consequence of the UCPCR positivity, antibody negativity and dominant family history, genetic testing was undertaken. A heterozygous mutation in *HNF1A* was identified and a diagnosis of HNF1A MODY was confirmed in Daniel.

This correct molecular genetic diagnosis enabled Daniel to stop his insulin treatment and transfer to a low dose of sulphonylurea with improvements in quality of life. Family testing confirmed that both his mother and maternal grandfather were also heterozygous for the HNF1A mutation and therefore also had HNF1A MODY, and this diagnosis enabled them to change on to the most appropriate treatment with improvements in glycaemic control.

Introduction

Maturity onset diabetes of the young (MODY) is initially misdiagnosed as Type 1 or Type 2 diabetes in approximately 80% of cases resulting in inappropriate treatment and follow up (1-7). MODY is characterised by three key features: i) diabetes typically diagnosed less than 25 years in at least one family member, ii) autosomal dominant inheritance (with diabetes in a parent or child) and iii) non-insulin dependent diabetes (or evidence of significant endogenous insulin production more than three years post diagnosis) (8). However the significance of these features may not be appreciated by healthcare professionals, leading to incorrect diagnosis and treatment. Poor recognition results in mean delays of >9 years from diabetes diagnosis to specific molecular genetic diagnosis, in many cases leading to years of unnecessary insulin treatment (9). Early diagnosis of MODY is important as transfer from insulin to sulphonylurea is less likely to be successful with increasing duration of diabetes (10)

Biomarker tests (islet autoantibodies and C-peptide) can help identify appropriate candidates for genetic testing for MODY, or other forms of monogenic diabetes, avoiding reliance on clinical recognition (11, 12). As these tests are not routinely used in clinical practice, identifying individuals diagnosed with diabetes below the age of 25 years with an affected parent or child may be a useful first step in detecting some of those in whom further testing may be warranted (Table 1). However islet autoantibody and C-peptide tests are cheap and easily available and can aid differential diagnosis (11-14). The free online MODY probability calculator or Diabetes Diagnostics App can also be used to identify those with a higher probability of having MODY <http://www.diabetesgenes.org/content/mody-probability-calculator> (15).

This article provides some background on islet autoantibody, C-peptide and genetic tests for use in individuals with diabetes, including what samples are required, practical points to consider and where to find additional information.

Islet autoantibodies

Type 1 diabetes results from an autoimmune mediated destruction of the insulin producing pancreatic beta cells. Autoantibodies recognizing the islet cell antigens glutamic acid decarboxylase (GAD65), insulinoma antigen 2 (IA-2) and Zinc Transporter 8 (ZnT8) are present in up to 90% of newly diagnosed patients with Type 1 diabetes (16). Most individuals with Type 1 diabetes will have multiple islet autoantibodies detectable in their blood at diagnosis and less than 10% will have only one detectable antibody when assessed in combination (11).

Testing islet autoantibodies could be considered the most helpful investigation to differentiate Type 1 diabetes from MODY (11). The prevalence of GAD, IA-2 & ZnT8 autoantibodies is less than 1% in GCK, HNF1A and HNF4A MODY, and testing close to diagnosis gives very good discrimination of Type 1 diabetes from MODY (11). The difference in prevalence of autoantibodies between Type 1 diabetes and MODY means these tests are useful in aiding differential diagnosis and identifying patients who may benefit from genetic testing. Although antibody testing close to diagnosis is recommended, GAD and IA2 remain detectable for many years and show high levels of diagnostic accuracy (17). Testing multiple antibodies is important as multiple antibody positivity increases the certainty of Type 1 diabetes and significantly increased the proportion of patients with a detectable antibody from approximately 60% with GAD only to over 80% with GAD and IA-2(11). Islet cell autoantibodies (ICA) was the first method for detecting islet autoantibodies. ICA identifies the presence of human antibodies that bind to rodent or monkey pancreatic tissue, however the test is non standardised and the sensitivity can be as low as ~10% (i.e. 9/10 with Type 1 diabetes have a negative result), ICA antibodies also disappear rapidly after diagnosis. ICA has now mostly been abandoned because of a poor diagnostic accuracy. Insulin autoantibodies (IAA) also have a lower sensitivity and as soon as exogenous insulin is given this is no longer a useful test. Therefore we recommend testing GAD, IA-2 and ZnT8 in combination.

Local laboratories may test for autoantibodies but it is important to establish which tests they offer. ICA antibodies are not recommended as they are measured using a non standardised assay, have low reproducibility, low sensitivity and disappear rapidly after diagnosis (18) (See appendix 1 available online at www.practicaldiabetes.com for further detail).

Islet autoantibodies are most useful in enabling a firm diagnosis of Type 1 diabetes to be made in those who are antibody positive. This obviates the need for genetic testing as they are unlikely to have monogenic diabetes and if two antibodies are positive genetic testing is not indicated (11). Those previously considered to have Type 1 diabetes who are antibody negative should be considered for genetic testing, particularly if they have other features that would raise suspicion of MODY, for example a parent with diabetes or detectable levels of C-peptide.

C-peptide

C-peptide is made in equimolar amounts to insulin and is typically tested in patients on insulin treatment to assess endogenous insulin secretion. Its role in individuals not on insulin treatment is limited. Those with long standing Type 1 diabetes typically have low or undetectable levels (<200 pmol/L) indicating insulin deficiency (12). C-peptide may be present during the honeymoon period in Type 1 diabetes so when used to aid differential diagnosis is best measured at least 3 years post diagnosis (19).

Historically C-peptide was considered difficult to measure as it was previously recommended that the blood samples should be collected on ice, centrifuged immediately, and taken to the laboratory within 30 minutes (20), making the tests impractical within the general clinic setting. However urinary C-peptide creatinine ratio (UCPCR) is a simple, reliable, non-invasive measure which is stable for three days at room temperature (12,13). UCPCR can be measured on a post prandial sample taken approximately two hours after a meal stimuli, to identify the presence of endogenous insulin (21). This could either be taken two hours after the largest carbohydrate containing meal of the day and posted from home, or a random non fasting sample taken at a clinic visit (likely to be post breakfast or post lunch). Samples should be taken in a boric acid tube and may be tested locally, or sent to the Exeter laboratory at the Royal Devon and Exeter NHS Foundation Trust. UCPCR costs <£12 <http://www.exeterlaboratory.com/test/c-peptide-urine/> (Table 2). More recently it has been shown that plasma C-peptide is more stable than previously thought and there is no degradation within the first 24 hours on whole blood at room temperature when collected on EDTA (22). This presents another opportunity for easy and pragmatic assessment of endogenous insulin production on a blood sample collected in primary care or at a routine clinic visit.

If the C-peptide result is 'out of keeping' with other clinical findings then the test should be repeated, especially if the result is unexpectedly low. Patients 'tipping out' boric acid preservative from the urine collection tube, or a sample taking more than 3 days to reach the laboratory can result in artificially low results (13). The interpretation of C-peptide levels depends on the specific clinical scenario i.e. type of diabetes and treatment. However UCPCR levels <0.2nmol/mmol, or stimulated blood C-peptide <200pmol/l, outside the honeymoon period indicate insulin deficiency which supports a diagnosis of Type 1 diabetes. UCPCR ≥0.2nmol/mol indicates endogenous insulin and has been used to differentiate patients with MODY from Type 1 diabetes >5 years post diagnosis (14). In those with a diabetes duration >3 years with significant endogenous insulin an alternative diagnosis to Type 1 diabetes should be considered.

Most of the studies of UCPCR have been performed in patients with normal renal function (eGFR >60 mL/min/1.73 m²) but it has been validated in patients with Type 2 diabetes with moderate renal impairment (eGFR 30-60 mL/min/1.73 m² (23). However the test is not appropriate in patients with severe renal impairment.

Online MODY probability calculator / Diabetes Diagnostic App

Prior to genetic testing clinical details should be entered into the online MODY probability calculator (<http://www.diabetesgenes.org/content/mody-probability-calculator>) to establish the likelihood of MODY in each particular case. This takes into consideration other factors such as parental family history, initial and current treatment, gender, BMI, current age and age at diagnosis. These tools are for use in patients diagnosed with diabetes under the age of 35 and were developed on a European Caucasian cohort.

There is no specific recommended probability 'cut off' for proceeding to genetic testing. The current pick-up rate for MODY testing in the UK is 25%, but where a diagnosis would make a difference to a patient's management, testing might still be considered appropriate at a lower probability.

The Diabetes Diagnostics app is available for free download and combines the MODY clinical prediction calculator, information from national and international diabetes guidelines, and expert opinion from world leaders in monogenic diabetes to provide a resource to help guide diabetes classification. The app also includes data regarding other features that may be associated with different causes of monogenic diabetes (eg. Renal cysts) (see Table 3).

Genetic testing for MODY

In individuals, previously thought to have Type 1 diabetes, diagnosed <25 years of age who are islet autoantibody negative and C-peptide positive >3 years post diagnosis, an alternative diagnosis and genetic testing should be considered.

The molecular genetic laboratory at the Royal Devon and Exeter NHS Foundation Trust carries out genetic testing for all known causes of MODY. EDTA whole blood (minimum 3ml) or genomic DNA samples (minimum 5ug) are required and should be sent at room temperature in the post (complying UN3373 postage requirements <http://www.un3373.com/info/regulations/>) along with a completed diagnostic request form (available to download at http://www.diabetesgenes.org/sites/default/files/mody_request_form.doc (Table 2). See appendix 1 available online at www.practicaldiabetes.com for further detail.

Conclusion

Identifying individuals with monogenic diabetes is essential to ensure they receive optimal treatment. The correct molecular genetic diagnosis also enables follow up of family members and counselling regarding risk to their unaffected children. Non genetic tests (autoantibodies and C-peptide) should be considered in individuals diagnosed below 25 years of age with an affected parent or child. These tests are cheap and easy to perform and, in combination with the online MODY probability calculator or Diabetes Diagnostics App, can help identify those in whom genetic testing may be appropriate. More information on diagnosing MODY, the tests available and the national network of Genetic Diabetes Nurses can be found on www.diabetesgenes.org.

Declarations

There are no conflicts of interest to declare

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Table 1. When to consider monogenic diabetes

Consider monogenic diabetes in those with:	Notes
Diabetes diagnosed less than 6 months of age	Free genetic testing for all patients diagnosed <6 months of age (whatever their age now) http://www.diabetesgenes.org/content/genetic-testing-neonatal-diabetes
Diabetes diagnosed < 25 years with an affected parent or child	Consider antibodies, c-peptide (in insulin treated patients) and enter details into MODY probability calculator / App prior to genetic testing http://www.diabetesgenes.org/content/mody
Diabetes (young onset) plus other features associated with rare forms of monogenic diabetes	Identify features associated with rare monogenic causes of diabetes and consider referral for genetic testing http://www.diabetesgenes.org/content/information-known-types-rare-diabetes

Table 2. Tests aiding differential diagnosis of diabetes

Test	Analyte	Sample collection	Why test ?	When to test	NHS cost	Reporting time	Result interpretation	More information
Islet autoantibodies	GAD, IA2, ZnT8	Clotted blood (1 x 7.5ml) for GAD, IA-2, ZnT8 only or EDTA whole blood (10ml adults; 5ml children; 1ml neonates) if DNA extraction for MODY testing is also required	To differentiate between T1D and non T1D	Ideally close to diagnosis but can still be positive many years post diagnosis	£29.00	10 working days	Positive to 1 or more antibodies supports a diagnosis of Type 1 diabetes.	http://www.exeterlaboratory.com/test/gad-antibodies/
C-peptide	1. Blood C-peptide 2. Urinary C-peptide creatinine ratio (UCPCR)	Non fasting random sample in EDTA In Boric acid container, sample 2 hours after largest meal of the day, having emptied bladder before eating	To differentiate between T1D and non T1D	At least 3 or ideally more than 5 years post diabetes diagnosis	£12.00	5 working days	C-peptide > 200pmol/L or UCPCR >0.2nmol/mol indicates endogenous insulin production	http://www.exeterlaboratory.com/test/c-peptide-plasma/ http://www.exeterlaboratory.com/test/c-peptide-urine/
Genetic testing	For individual MODY genes (e.g. <i>GCK</i>) or all known MODY genes in one test (tNGS)	5-10ml venous blood in EDTA or >5µg DNA posted at room temperature. For mitochondrial diabetes testing only: Urine sample in a sterile white top universal container (from first pass urine of the day)	To differentiate between T1D, T2D or monogenic diabetes	At any time, although an earlier diagnosis will mean optimal treatment initiated earlier	£75-£650 depending on testing performed.	Individual genes - 3 weeks tNGS - 6 weeks	Positive genetic test confirms specific MODY subtype which has implications for treatment and testing of family members.	http://www.diabetesgenes.org/content/diagnostic-tests-available http://www.diabetesgenes.org/content/new-test-all-mody-genes

tNGS = Targeted Next Generation Sequencing (of all known MODY genes)

Table 3. Additional features associated with the commonest causes of monogenic diabetes

Gene	Other features associated with the commonest causes of monogenic diabetes
HNF1A MODY	Low renal threshold for glucose Sensitive to low dose sulphonylureas Early myocardial infarction
HNF4A MODY	Sensitive to low dose sulphonylureas Macrosomia Neonatal hypoglycaemia
Glucokinase MODY	Mild stable hyperglycaemia: FBG 5.5-8mmol/L, HbA1c 40-60mmol/mol, small post-prandial increase in blood glucose (2 hour OGTT increment of <3mmol in 70% of GCK MODY cases).
HNF1B MODY	Renal cysts or other renal developmental abnormality Low magnesium Low faecal elastase due to pancreatic hypoplasia Urogenital tract abnormality e.g. bicornuate uterus Early onset gout Autism (in those with whole gene deletions)
Maternally inherited diabetes and deafness (MIDD)	Maternally inherited diabetes Bilateral sensorineural deafness Short stature

Appendix 1 – Accessing tests aiding differential diagnosis: Royal Devon and Exeter NHS Foundation Trust

Islet autoantibodies

The Blood Sciences department at the Royal Devon & Exeter NHS Foundation Trust offers a highly sensitive, automated ELISA method for the quantitative determination of GAD, IA-2 & ZnT8 autoantibodies in both serum and plasma samples for under £30 <http://www.exeterlaboratory.com/test/islet-cell-antibodies/> with results typically reported within ten working days (see Table 2 main article). Clotted samples should be sent if antibody testing only is required, but EDTA samples allow testing of antibodies and storage of DNA for subsequent MODY genetic testing if antibodies are negative, without the need for additional samples. Local laboratories may test for autoantibodies but it is important to establish which tests they offer. ICA antibodies are not recommended as they are measured using a non standardised assay, have low reproducibility, low sensitivity and disappear rapidly after diagnosis (18).

C-Peptide

The Blood Sciences department at the Royal Devon & Exeter NHS Foundation Trust accepts referrals for the analysis of urine c-peptide creatinine ratio (UCPCR). Urine should be collected in a boric acid container. The sample should be taken 2 hours after eating the largest meal of the day, having emptied the bladder before eating. The samples are stable for 3 days at room temperature and cost of testing is around £12 <http://www.exeterlaboratory.com/test/c-peptide-urine/>

Alternatively plasma c-peptide can also be measured <http://www.exeterlaboratory.com/test/c-peptide-plasma/>

Genetic testing for MODY

Individual genes can be tested if the clinical characteristics clearly suggest a particular type of MODY (for example if a patient has persistent fasting hyperglycaemia in the range of 5.5-8mmol/L, small post prandial increase in blood glucose and HbA1c always between 40-60mmol/mol then a diagnosis of GCK MODY is highly likely and testing for the *GCK* gene alone could be requested) (see Table 3 main article). The cost of testing individual genes varies from £75 for maternally inherited diabetes and deafness (MIDD) to £350 for *GCK* or *HNF1B* and £450 for combined *HNF1A* and *HNF4A* sequencing. However if the phenotype is not obvious it is preferable to request simultaneous analyses of all known MODY genes in a single test using targeted next generation sequencing (tNGS) at a cost of £650. The simultaneous testing of multiple genes by NGS increases the number of patients in whom a monogenic form of diabetes is identified (24). NGS testing also removes the need for detailed clinical phenotyping in order to determine which subtype of MODY the patient

should be tested for. Results are usually available within 3 weeks for single gene tests or 6 weeks for tNGS, but samples can be prioritised for rapid result turnaround in specific circumstances (e.g.pregnancy). A genetic diagnosis of MODY is made in approximately 20-25% of patients referred for MODY genetic testing in the UK. Novel, previously unreported genetic variants are frequently identified in MODY genes (accounting for approximately 60% of all variants identified (25,26) and these require detailed investigation by clinical scientists to determine their clinical significance. Referring clinicians have a key role to play in variant interpretation through gathering additional clinical information and recruiting family members for co-segregation studies. Support can be provided by the local Genetic Diabetes Nurse <http://www.diabetesgenes.org/content/genetic-diabetes-nurses-locations-map> .